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Painful Diabetic Neuropathy is More than Pain Alone: Examining the Role of Anxiety and Depression as Mediators and Complicators

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Abstract A wealth of information exists regarding the plight of patients suffering with diabetic peripheral neuropathic pain (DPNP). Although physical pain is certainly a primary challenge in the management of this condition, disorders associated with emotional pain—especially depression and anxiety—also greatly complicate the clinician's efforts to attain optimal outcomes for DPNP patients. This article reviews the high rate of comorbidity between DPNP and depression/anxiety with a focus on why this pattern of comorbidity exists and what can be done about it. To accomplish this, the many physiologic similarities between neuropathic pain and depression/anxiety are reviewed as a basis for better understanding how, and why, optimal treatment strategies use behavioral and pharmacologic modalities known to improve both physical pain and symptoms of depression and anxiety. We conclude by highlighting that screening, diagnosing, and optimally treating comorbid depression/anxiety not only improves quality of life, these but also positively impacts DPNP pain.

Keywords Diabetes mellitus · Diabetic peripheral neuropathic pain (DPNP) · Major depression · Depressive symptoms · Anxiety · Prevalence · Inflammation · Peripheral nerves · Central sensitization · Kindling · Serotonin reuptake inhibitors · Serotonin-norepinephrine reuptake inhibitors · Duloxetine · Pregabalin · α-2-δ ligands · Tricyclic antidepressants · Psychotherapy, Cognitive behavior l therapy · Screening instruments

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Introduction

In the past few months, the appearance of articles with a title such as *"Diabetes and depression – a risky combination"* [1] have alerted clinicians to the nefarious relationship that exists between psychiatric illnesses and diabetes. Depression/anxiety and diabetes will surely rank among the defining epidemics of the 21st century, given the current explosion in the prevalence rates of both conditions in both the developed and developing worlds. A collision between such highly prevalent disorders is to be expected; yet it

appears that these disorders associate in ways that transcend mere coincidence, and that, in fact, there are numerous biological reasons why diabetes and depression/anxiety increase each other's prevalence, and compound the impairment associated with each disorder. For example, diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes. Interestingly, pain is also a frequent symptom of both depressive and anxiety disorders. Emerging data demonstrate that in patients with DPNP, the presence of depression/anxiety worsens pain and negatively impacts treatment. In fact, the more pain perceived by a patient as a result of DPNP, the poorer will be his or her mental health [2•]. In other words, depression and anxiety are more than just emotional disorders, and DPNP is more than just a pain condition. In patients with DPNP, depression and anxiety commonly coexist and act as mediators and complicators of eventual outcomes. Fortunately, optimized treatment of depression/anxiety can positively impact both the pain and functioning of patients afflicted with DPNP.

How Common is the Overlap Between Diabetes and Depression/Anxiety?

It is important to realize that psychiatric illnesses are common in our society in general, and in clinical populations in particular, with prevalence rates that appear to be increasing with the passage of time. A large US-based survey put the lifetime prevalence of major depression at 12.7% and any anxiety disorder at 19.2% [3]. More recent prevalence data from epidemiologic surveys unfortunately show that mental illnesses continue to have an upward trajectory. Moreover, the World Health Organization has estimated depression to be one of the world's leading disabling conditions [4].

As with depression and anxiety, prevalence rates of diabetes and its complications have increased explosively in the last half century [5, 6]. Because of this, it should come as no surprise that clinicians see these conditions repeatedly, and see them intertwined more often than not. A recent survey of US adults found the overall age-adjusted prevalence of anxiety to be 10.9% in people without diabetes compared to 19.5% in those with diabetes. Even after adjusting for educational level, marital status, employment status, current smoking, leisure time, physical activity, and body mass index, people with diabetes had a 20% higher prevalence of a lifetime diagnosis of anxiety [7•]. Depression has often received the lion's share of attention from clinicians, but anxiety disorders are very common in the context of diabetes. In fact, in one recent study anxiety disorders were actually found to be more prevalent than depression in diabetes, with 32% of patients meeting the threshold for anxiety disorder and 22.4% for depression [8]. This replicates findings from a previous study that also found anxiety disorders to be at least as frequent, if not more so, than depressive disorders in DPNP patients [9.]

As with anxiety, there is considerable overlap between DPNP and depression. In 2001, a meta-analysis of extant literature (27 studies, 5374 patients) that examined the relationship between depression and DPNP found a significant and positive relationship between the two conditions (effect size=0.25). Of concern, depression was associated with a number of diabetic complications, including retinopathy, nephropathy, macrovascular complications, sexual dysfunction, and neuropathy [10]. Studies conducted in the past decade have replicated these findings of high prevalence of depression in patients with diabetes [9, 11, 12]. Moreover, the complex relationship between diabetes and anxiety/depression is not just observed here in the United States, but also in other parts of the world [13]. A recent study from the United Arab Emirates found high rates of mental distress in diabetic patients and found that peripheral neuropathy was a correlate of poorer mental health [14]. A recent study from India found a similar relationship between depression and neuropathy in individuals suffering from diabetes, with depression increasing the odds of neuropathy with an odds ratio of 1.94 [15].

What Impact Does this Overlap Have on the Lives of Patients?

One word summarizes the impact of depression and anxiety on outcomes in diabetic patients: significant. The presence of anxiety and/or depression leads to poorer outcomes for micro- and macrovascular complications of diabetes, with pain and physical mobility being added complications [11]. An additional complication of having depression and/or anxiety is that diabetic patients with these comorbidities are less compliant with self-monitoring, keep fewer appointments with primary care clinicians, exercise less, and have lower dietary adherence [16, 17]. Cardiovascular risk factors are clearly elevated in patients with diabetes who also screen positive for depression [18]. Additionally, depressed diabetic patients are at increased risk for metabolic syndrome, higher waist circumference, and increased triglycerides—all factors known to worsen outcomes for depression [19]. As stated above, neuropathy also appears to occur at elevated rates when depression complicates diabetes [20]. Anxiety does not appear to take a backseat to depression in its ability to produce poorer outcomes when it is comorbid with diabetes. Patients with diabetes and anxiety were found to have poorer glycemic control and less frequent blood glucose monitoring [21].

And finally, neuropathy has been found to be independently associated with depression in diabetic patients [13].

The impact of comorbid depression/anxiety in patients with diabetes is also financial [22]. A recent study of Medicare-insured patients with diabetic neuropathy and depression and/or anxiety found an increase of $9235 in total health care costs compared with patients who only had diabetes. Commercially insured patients with depression and/or anxiety comorbid with diabetes also cost more than patients with diabetes alone, with a cost differential of $10,389 [23]. Although cross-sectional studies have shown for some time that having depression and/or anxiety negatively impacts outcomes for diabetic patients, we now have high-quality prospective data demonstrating that complications of diabetes are significantly and negatively impacted by comorbid depression [24]. Moreover, the impact of comorbid depression on diabetes is felt not just on individual complications of diabetes, but on general quality of life [25]. Finally, just as anxiety/depression negatively impact diabetic complications, it is equally important to keep in mind that the reverse is also true: diabetic complications can powerfully increase depression/anxiety with all their attendant disabilities. Nowhere is this seen more clearly than in data showing that the degree of pain experienced by DPNP patients directly impacts their functioning and that increasing levels of pain are also linked to increases in depressive and anxiety symptoms [9].

Does Emotional Stress Cause Diabetes (and Therefore its Complications)?

This is a provocative question, no doubt. And the answer is even more provocative, in that there is growing evidence from a number of well-designed, prospective epidemiologic trials that emotional stress (and depression and anxiety are conditions associated with significant emotional stress) may increase an individual's chances of developing diabetes [26••]. Furthermore, there are recent data suggesting a bidirectional relationship between depression and diabetes, such that no matter which condition develops first, it sets the stage for the arrival of the other disorder [27•, 28, 29]. A natural question that's raised at this point is, why? Why is there a potential bidirectional relationship between diabetes and depression and/or anxiety? We will explore the potential links and offer explanations in the neurobiology section that follows.

Shared Neurobiology of DPNP and Depression/Anxiety

DPNP occurs in context of both type 1 and type 2 diabetes [30]. Numerous abnormalities associated with diabetes likely contribute to its occurrence [30]. DPNP initially takes on a "glove and stocking distribution" that eventually progresses from toes and feet upward to involve increasingly large areas of the body. It is important at this juncture to emphasize that etiologic factors that initiate peripheral nerve damage do not necessarily overlap with the ones that are responsible for the key feature of DPNP, such as central sensitization caused by maladaptive neuroplastic changes [31].

Both peripheral and central sensitization play important roles in producing the signs and symptoms of DPNP. Unfortunately, there are very few human studies characterizing biomarkers for DPNP, especially ones that might differentiate painful- from non-painful diabetic neuropathy. Therefore, preclinical studies are our main source of information about the pathophysiology of peripheral sensitization in the context of DPNP [31]. One of these preclinical studies has recently found a greater increase in inflammatory and endothelial dysfunction markers in painful- relative to non-painful diabetic neuropathy [32•]. Emerging evidence suggests that peripheral nociceptive neural tissue damage may be caused by a sustained local inflammatory response. This response promotes the development of an "inflammatory soup" that surrounds nociceptive nerve endings [31, 33, 34, 35•]. Many of the molecules in this "inflammatory soup" bind to G-protein-coupled receptors on nerve cells and induce protein kinases. The ensuing cascade of intracellular events leads to increased production and membrane insertion of ion channels and receptors that alter the signaling characteristics of nociceptive neurons. This causes the activation threshold for pain neurons to be substantially reduced, inducing them to fire more easily. This spontaneous and ectopic firing of the peripheral nociceptive fibers is the hallmark of peripheral sensitization [31, 33, 34, 35•]. These facilitated and amplified pain signals are subsequently propagated to dorsal root ganglia, and eventually to dorsal horn neurons and from there to the brain.

There is very little preclinical evidence differentiating the pathophysiology of DPNP at the central nervous system (CNS) level from non-painful diabetic neuropathy, or from other forms of neuropathic pain [31, 32•]. In fact, central sensitization is a pathophysiologic mechanism shared by chronic neuropathic, inflammatory, and dysfunctional pain [31].

Allodynia and secondary hypersensitivity, which are characteristic features of central sensitization, appear to be mediated by synaptic strengthening and neuroplastic changes at multiple CNS levels [31]. At the level of dorsal horn of the spinal cord, pathologically sensitized C-fiber and A-δ fiber inputs lead to significant synaptic changes in dorsal horn neurons [36]. The combination of excessive incoming pain signals conveyed by glutamate binding to *N*-

methyl-D-aspartate (NMDA) receptors, substance P, neurotrophic factors, and inflammatory mediators (including cytokines, chemokines, and prostaglandins) alters the delicate signaling balance that typically exists between, astroglia, microglia, γ-aminobutyric acid interneurons, and dorsal horn neurons [34, 35•, [36–39]. These signaling alterations promote second-order changes in postsynaptic dorsal horn neurons that are manifested by alterations in the density, activity and membrane insertion of NMDA receptors, enhanced synthesis of ion channels, and structural proteins [34, 35•, 36, 38–40]. The cumulative effect of these alterations translates into long-term potentiation, which is the most important neurobiological substrate of central sensitization [35•, 39].

Current scientific evidence emphasizes central sensitization as a fundamental feature of all forms of neuropathic pain [31, 41, 42]. Interestingly, conditions such as depression/anxiety, which are characterized by emotional pain, may also be driven by physiologic processes similar to central sensitization. For example, major depression is widely considered to be associated with a "kindling" phenomenon. In the context of depression, kindling implies that each episode of depression makes subsequent depressive episodes more likely and less dependent upon an external impetus such as stress or sickness [43]. Robert Post [44]—who initially introduced kindling as an explanatory construct to account for the tendency of mood disorders to worsen over time—has recently proposed that kindling and sensitization may have similar neurobiological underpinnings, such as neuroplastic changes and alterations in gene expression. In the same vein, other authors have gone so far as to suggest "neurosensitization" as a common etiology for chronic pain, depression, and anxiety disorders [45].

In addition to peripheral and central sensitization, neuropathic pain is also characterized by altered limbic and cortical function and structure [41, 46, 47]. The brain circuitry involved in pain modulation (often referred to as "the pain matrix") shares elements with brain networks responsible for the modulation of mood and the stress response [48–54].

Neuroimaging studies of neuropathic pain are not nearly as numerous as those focusing on major depression. Nevertheless, functional MRI (fMRI) studies of neuropathic pain have implicated the same brain areas known to be functionally abnormal in chronic non-neuropathic pain, such as prefrontal cortex, thalamus, insula, and anterior cingulate cortex (ACC) [47, 52]. Apkarian et al. [55] conducted volumetric MRI to assess gray matter changes in a group of chronic back pain (CBP) sufferers, the majority of whom experienced pain of neuropathic origin. These investigators found significantly reduced gray matter volume in dorsolateral prefrontal cortex (DLPFC) and thalamus of CBP patients relative to controls. Furthermore, decreased gray matter density in DLPFC correlated with pain intensity, duration, and negative emotional characteristics in this population. Additionally, the magnitude of gray matter reduction in CBP patients was equivalent to 10 to 20 years of normal aging. Considering the well-established role of DLPFC in top-down regulation of limbic and paralimbic prefrontal areas [35•], it is conceivable that morphologic changes in DLPFC may contribute to the compromised emotional and pain modulation apparent in many neuropathic pain patients [55].

In another recent study, a group of diabetic patients was compared with healthy controls using magnetic resonance spectroscopy [56]. Diabetic subjects had decreased brain *N*-acetyl aspartate (NAA) levels relative to the control group. Moreover, diabetic subjects suffering from pain had a greater reduction of NAA in thalamus than subjects who had diabetes but no pain [56]. These findings suggest that diabetes on its own maybe associated with metabolic changes in DLPFC [35•, 56]. Additionally, significant reduction in thalamic NAA in diabetic subjects suffering from pain compared with ones who are pain free may imply greater functional disturbances in these patients that result in altered perception and pain amplification [56•].

Another group of investigators used fMRI to study functional connectivity between brain areas in patients suffering from DPNP [57]. Activity in several cortical areas including the fusiform gyrus, left inferior temporal gyrus, and dorsal ACC negatively correlated with pain, whereas activity in DLPFC, both insulae, and thalamus showed a positive association with the experience of pain. This was the first functional study to characterize aberrant default mode functional connectivity in the context of spontaneous diabetic neuropathic pain. In a subsequent study the same group found disruption in thalamocortical processing in patients suffering from DPNP relative to healthy controls [58]. Given the multiple overlaps observed between depression and neuropathic pain it is not surprising that similar functional and structural changes in amygdala and hippocampus have been described in major depressive disorder and neuropathic pain [59–62].

Altered function of these limbic-cortical circuits is believed to lead to disruptions in neuroendocrine, autonomic, and immune regulation that may further contribute to the initiation and/or worsening of mood and pain symptoms [41, 46, 53, 63]. Emerging evidence suggests that a combination of excessive sympathetic activity and elevated proinflammatory cytokine production and release likely plays a role in the etiology of both depression and neuropathic pain [35•, 64]. Furthermore, major depression and neuropathic pain are both associated with disturbed neuron-glia relationships, alterations in glutamatergic and intracellular signaling cascades, and neurotrophic trafficking [34, 65–69].

Thus, disrupted neuroimmune, neuroendocrine, and autonomic homeostasis may interact to perpetuate states of pain and depression [35•, 70]. Peripheral markers of the stress may not only contribute to the clinical manifestations of depression/anxiety and neuropathic pain but may also perpetuate disturbances in the regulation of cortical-limbic circuitry, thereby maintaining a vicious cycle (Fig. 1) [35•, 64, 70, 71]. Finally, major depression and DPNP may be best conceptualized as conditions composed of combined psychosomatic components (ie, brain driving bodily deregulation) and somatopsychic components (ie, bodily processes promoting disruption of CNS homeostasis).

Screening for Depression and Anxiety in DPNP Patients

We have already established that rates of depression and/or anxiety are high in patients with diabetes, and particularly elevated when DPNP is present. There is a unified consensus that depression is commonly under-diagnosed in all settings, including in those clinics that see high numbers of diabetes-afflicted patients. Therefore, routine screening for depression and anxiety is recommended in all diabetic patients, young and old, newly diagnosed or previously diagnosed "established" patients, and type 1 and type 2 patients. We recommend three levels of

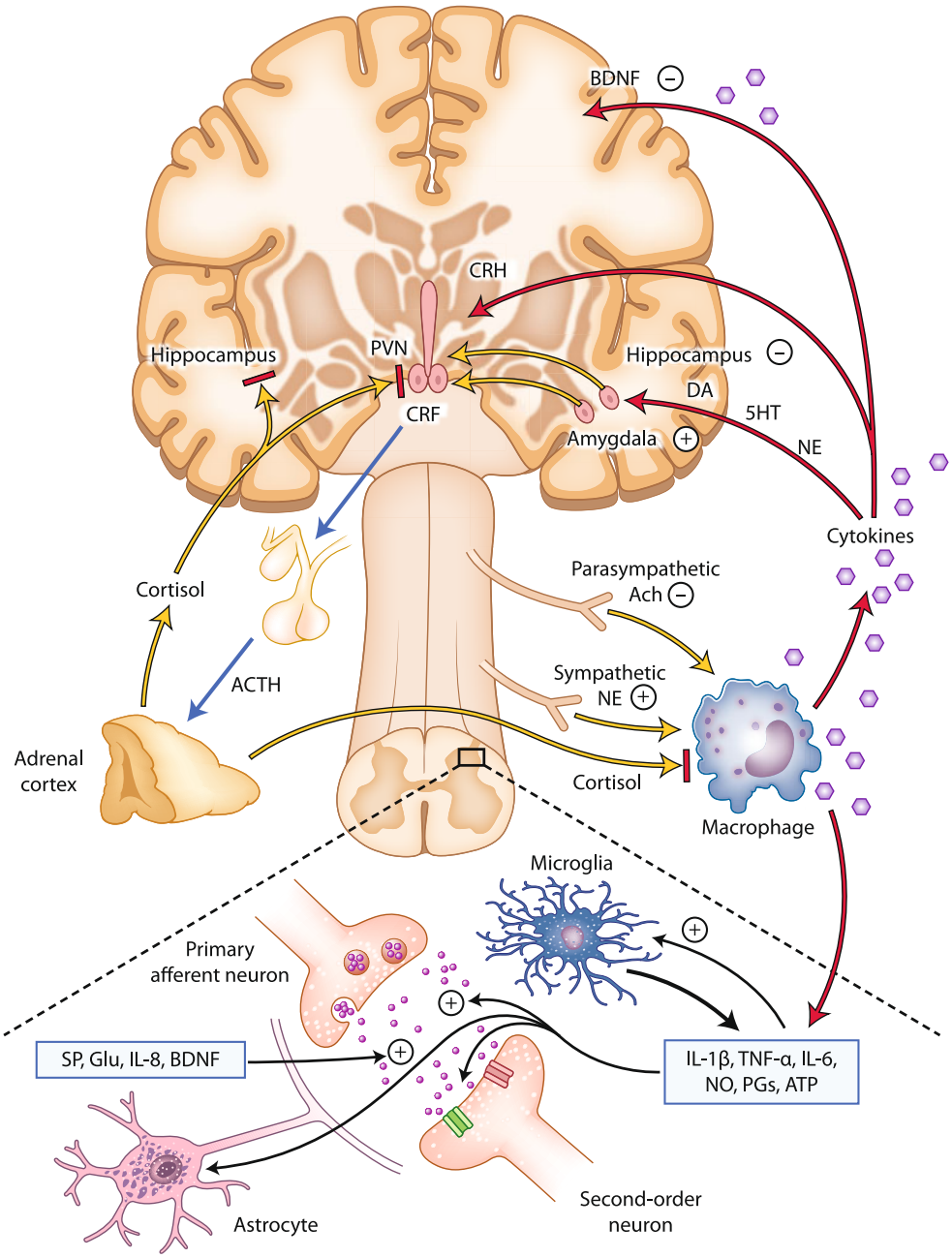

Fig. 1 MDD and DNeP may have shared systemic consequences. Compromised adaptive function of prefrontal cortical-limbic circuitry in MDD and DNeP interferes with autonomic, neuroendocrine, and neuroimmune regulation. Excessive sympathetic activity, combined with diminished parasympathetic tone, contributes to release of proinflammatory cytokines (eg, TNF-α, IL-1, IL-6) from macrophages and other immune cells. Activated microglia exchange signals with astrocytes and nociceptive neurons, amplifying pain-related transmission of Glu, SP, ATP, BDNF, proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, NO), and PGs. *Ach* acetyl choline; *ACTH* adrenocorticotropic hormone; *ATP* adenosine triphosphate; *BDNF* brain-derived neurotrophic factor; *CRF* corticotropin-releasing factor; *CRH* corticotropin-releasing hormone; *DA* dopamine; *DNeP* diabetic neuropathic pain; *Glu* glutamate; *5HT* serotonin; *IL* interleukin; *MDD* major depressive disorder; *NE* norepinephrine; *NO* nitrogen oxide; *PGs* prostaglandins; *PVN* paraventricular nucleus of hypothalamus; *SP* substance P; *TNF-α* tumor necrosis factor-α. (*Modified from* Maletic and Raison [35•])

screening. Step 1 is asking the patient directly about the presence of symptoms of depression and anxiety (Table 1). Step 2 is to collect collateral information from spouse, family, friends, previous and other health care providers. This can be very valuable. Step 3 is to use screening tools that can help detect depression and anxiety.

To screen for depression we would like to recommend a specific tool that has been studied in diabetic patients, the PHQ-9 (Physical Health Questionnaire-9) [72]. It has demonstrated good psychometric properties in diabetic patients [73]. Another instrument we find useful is the HADS (Hospital Anxiety and Depression Scale), which has also been used for screening purposes in studies of diabetic patients [74, 75]. A specific questionnaire for generalized anxiety disorder is GAD-7 (Generalized Anxiety Disorder-7) [76, 77]. A few words of caution: these instruments are not diagnostic; their main purpose is to screen (and to use as a measurement tool for response assessment after treatment has been initiated). Therefore, the clinician should not assume that elevated scores on PHQ-9, GAD-7, or HADS automatically suggest a psychiatric diagnosis, as some symptoms of diabetes can mimic the symptoms of anxiety or depression on these scales [78•]. Despite these potential weaknesses, scales such as the ones we recommend are highly useful, and we strongly recommend that diabetologists develop familiarity with them and use them on a regular basis. For further details on these three screening instruments, please refer to Table 2.

Treatment Options

An integrated treatment approach to treating patients with DPNP and depression/anxiety is recommended, with the treatment team including (depending on the individual patient's needs) a diabetic medicine specialist, primary care clinician, psychiatrist, psychologist, social worker, diabetic education specialist, and dietician. The focus should be on addressing the following needs: improved control over mood and anxiety disorders, better glycemic control, better compliance with medications, appointments, exercise, and diet. One advantage of an integrated team approach is that it tends to promote an equal focus being placed on biological, environmental/social, and psychological issues [79–83].

Nonpharmacologic treatments are important components in the treatment of patents with DPNP and anxiety/depression. Convincing data demonstrate that cognitive behavioral therapy (CBT) is helpful either by itself or when combined with psychotropic medications in reducing symptoms of depression and anxiety. More recent data suggest that both motivational enhancement therapy and CBT can help improve suboptimal glycemic levels, suggesting that psychotherapeutic approaches may be beneficial not just for emotional issues, but may actually help actual core disease processes [84•, 85]. Given these findings, we feel the level of evidence supporting CBT's effectiveness in treating depression and anxiety is high enough that offering CBT to DPNP patients with depression and/or anxiety is appropriate. The fact that CBT has demonstrated helpfulness in improving glycemic control is an added benefit.

Pharmacologic therapies are often needed and indicated for patients with DPNP who also have depression and/or anxiety [86, 87]. We recommend against the routine use of selective serotonin reuptake inhibitors (SSRIs) as first-line agents in this patient population and strongly advise against the routine use of benzodiazepines. Our recommendation of not generally using SSRIs as first-line agents is based on a large dataset showing that these agents are not particularly effective in patients with comorbid pain and depression [88]. Our strong opposition to benzodiazepine for routine use as an anxiolytic or sedative is based on several factors, including their potential for addiction, gait disturbance with attendant increased fall risk, and memory impairment. These agents are also known to increase the risk for accidents [89, 90]. DPNP patients are typically ill-suited to

Table 1 DSM-IV symptoms of major depression and generalized anxiety disorder

Symptoms of major depression	Symptoms of generalized anxiety disorder
Sad mood	Excessive anxiety/tension
Irritable mood	Difficulty controlling the worry
Anhedonia (loss of pleasure)	Restlessness
Sleep disturbances	Fatigue
Appetite disturbances	Concentration/mind going blank
Psychomotor changes	Irritability
Helplessness/hopelessness	Muscle tension
Concentration/memory difficulties	Sleep disturbances
Fatigue/energy difficulties	
Suicidal thoughts	

In addition to a certain number of symptoms, impairment and duration criteria must also be met before a DSM-IV diagnosis is made.

(Adapted from Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [103].)

Table 2 Recommended screening tools for depression and anxiety

Name of scale	Used to assess	Patient or clinician rated	Scoring	Availability
GAD-7	-Generalized anxiety disorder	Patient rated	GAD-7 total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent cut-points for mild, moderate, and severe anxiety, respectively. When screening for anxiety disorders, a recommended cut-point for further evaluation is a score of 10 or greater	Public domain: http://www.phqscreeners.com/overview.aspx?Screener=03_GAD-7
PHQ-9	-Screening for depression -Sensitive to detect change in symptom severity in response to intervention	Patient rated	Total score ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe. and severe depression, respectively	Public domain: http://www.phqscreeners.com/overview.aspx?Screener=02_PHQ-9
HADS	Detects states of anxiety and depression	Patient rated	Anxiety and depression. None (0–7), borderline cases (8–10), definite cases (11 and above)	Copyrighted. Requires user fee for all users: http://shop.gl-assessment.co.uk/home.php?cat=417

GAD-7 Generalized Anxiety Disorder-7; *HADS* Hospital Anxiety and Depression Scale; *PHQ-9* Physical Health Questionnaire-9.

face these challenges and thus we recommend against the routine use of benzodiazepines. We also recommend against the use of tricyclic antidepressants (TCAs) as first-line agents in these patients. Our primary rationale for this recommendation is that the side-effect burden of TCAs is a cause of concern in many DPNP patients. These older antidepressants are best reserved for use as second- or third-line pharmacologic interventions. When these agents are used it is extremely important that this be done cautiously with close monitoring.

We recommend two classes of medications as first-line agents for patients with comorbid DPNP and depression/anxiety: serotonin norepinephrine reuptake inhibitors (SNRIs; for comorbid DPNP and depression) and α-2-δ ligand medications. SNRIs modulate both serotonin and norepinephrine and one of them, duloxetine, has separately demonstrated effectiveness in major depression, GAD, and DPNP, and has an approved indication for each of these disorders from the US Food and Drug Administration (FDA) [91–93]. Other SNRIs, such as venlafaxine, desvenlafaxine, and milnacipran are most likely effective too, but the evidence base for their effectiveness in patients with all these conditions at once is limited [94–97].

A-2-δ ligands induce their therapeutic effects by modulating calcium influx into neurons [98]. Two medications from this class are available for use: gabapentin and pregabalin. Particularly with pregabalin, there is established evidence in the literature of its effectiveness with DPNP [99] and GAD [100]. However, it is important to note that pregabalin has FDA approval for DPNP, but not GAD.

We would like to point out a significant shortcoming of the treatment literature in the area of DPNP comorbid with depression/anxiety. Although there are studies showing effectiveness of various agents in individual conditions (DPNP, anxiety disorders, depression), there is hardly any high-quality evidence for how these medications perform when a patient is comorbid for all these disorders, as so frequently happens in clinical practice. As a result, we are forced to extrapolate our recommendations for these comorbid patients from data from individual disease states. We are hopeful that in time high-quality pharmacologic studies will be conducted in patients with two, or even three coexisting disorders.

Clinical Recommendations

Based on data and experience, we feel that depression and anxiety disorders exist frequently in diabetic patients with DPNP. However, although challenging, the presence of diabetes along with depression should not be a barrier to good treatment outcomes for depression [101]. The pain of DPNP appears to be worsened and the impairment magnified when depression and/or anxiety coexists. As a diabetologist, we are certain your goal is to improve your patient's functioning as well as reduce suffering from all causes. We suggest, again based on data, that depression and anxiety disorders are both mediators and complicators of outcomes for your DPNP patients. There are complex, but increasingly better understood neurobiological reasons for this fact. We suggest routine screening for depression and anxiety in your DPNP patients. We recommend

increasing familiarity with screening tools such as HADS, PHQ-9, and GAD-7, and to use them routinely in your practice. They are quick, efficient, and reliable. If either or both disorders are detected, we suggest patient education, patient and family alliance building, and the offering of a judicious treatment plan that may include nonpharmacologic and/or pharmacologic options. Long-term, measurement-based care is recommended for DPNP patients who are also afflicted with depression and/or anxiety disorders. Finally, we recommend the institution of more widespread dissemination of this information through continuing medical education programs and other relevant means [102].

Conclusions

The past few years have produced a wealth of information and understanding regarding the plight of DPNP patients. Pain is clearly a major challenge and its management is a goal of treatment. In this article we have also attempted to alert you to the fact that depression and anxiety are also common in these patients and that these conditions complicate matters and impair outcomes. Numerous neurobiological threads tie diabetes, pain, depression, and anxiety together—these threads include the neuroendocrine system, autonomic system, and the inflammatory cytokine system, and a host of other, interrelated physiologic pathways in brain and body. Screening, diagnosing, and finally optimally treating the depression and anxiety not only improves a patient's quality of life, but these interventions also appear to impact the pain of DPNP patents.

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- •• Of major importance

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